Utility of Rapid Diagnostics in S. aureus Bacteremia in Antimicrobial Stewardship Programs

Jerod Nagel, PharmD, BCPS (AQID)
Pharmacy Team Lead, Infectious Diseases
Director Infectious Disease Residency
Clinical Assistant Instructor
Michigan Medicine
University of Michigan, College of Pharmacy

Disclosure Statement

I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.
Overview

- Review diagnostic technologies
- Diagnostic and clinical outcomes
- Incorporating diagnostics to comprehensive workflow to optimize results

### Staphylococcus aureus Bacteremia

**Table 1: Distribution of Rank Order of Selected Pathogens Associated with Healthcare-Associated Infections (HAIs) Reported to the National Healthcare Safety Network, by Type of HAI, 2009-2010**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall</th>
<th>CAUTI</th>
<th>NPC</th>
<th>SH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of pathogens</td>
<td>No. (%) of pathogens</td>
<td>Rank</td>
<td>No. (%) of pathogens</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2,671 (13.2)</td>
<td>2</td>
<td>3,725 (12.3)</td>
<td>2</td>
</tr>
</tbody>
</table>

**Notes:**
**Burden of Staphylococcus aureus Bacteremia**

- **15-30%** • Mortality
- **10-20%** • Endocarditis or metastatic disease
- **20-25%** • ICU admission
- **9-22 days** • Mean length of stay
- **40-71%** • ID consult

**Time to Effective therapy for S. aureus Bacteremia**

![Bar graph showing time to effective therapy for S. aureus bacteremia.](image)

- **33.3** (P=0.05) Delayed Therapy
- **19.3** (Early Therapy)
- **20.2** (Delay) vs. **14.3** (Early) (P=0.05)

*Clinical Infectious Diseases 2003; 36:1418–23*
Timeline for Organism Identification and Susceptibility Results

- Blood culture bottle
- Gram stain
- Automated Testing Set-Up
- Automated Organism ID
- Automated Susceptibilities

<table>
<thead>
<tr>
<th>Time from blood draw till microbiology results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram stain</td>
</tr>
<tr>
<td>Organism identification</td>
</tr>
<tr>
<td>Organism susceptibilities</td>
</tr>
</tbody>
</table>

Huang, Clin Infect Dis. 2014

Advances in Clinical Microbiology

- Mass spectrometry
  - MALDI-TOF
- Nucleic acid hybridization
  - PNA-FISH™
- Nucleic acid amplification
  - Real-time PCR, Multiplex arrays
- Magnetic resonance imaging
  - T2 Biosystems™
- Next generation whole genome sequencing
Culture and Sensitivity Timeline with Rapid Diagnostics

- **Microarray, PCR, PNA-FISH, MR, WGS**
- **Positive blood culture bottle**
- **Gram stain**
- **Automated Testing Set-Up**
- **Automated Organism ID**
- **Automated Susceptibilities**
- **Patient care team sees ID and susceptibility results**

**Targeted Organism ID & Detection of Genes Linked to Resistance**

**Nucleic Acid Amplification**

- **Nanosphere Verigene™**
- **Biofire Filmarray™**
  - Multiplex pcr product for GNR, GPC and Yeast
### Organism Resistance genes

<table>
<thead>
<tr>
<th>Organism</th>
<th>Resistance genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staph. aureus</em></td>
<td><em>MecA (MRSA)</em></td>
</tr>
<tr>
<td><em>Staph. epidermidis</em></td>
<td></td>
</tr>
<tr>
<td><em>Staph. lugdunensis</em></td>
<td></td>
</tr>
<tr>
<td><em>Strep. anginosis group</em></td>
<td></td>
</tr>
<tr>
<td><em>Strep. agalactiae</em></td>
<td></td>
</tr>
<tr>
<td><em>Strep. pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Strep. pyogenes</em></td>
<td></td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td><em>VanA,VanB, (VRE)</em></td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td><em>VanA,VanB, (VRE)</em></td>
</tr>
</tbody>
</table>

### Timeline for Organism Identification with Nucleic Acid Amplification Technology

- **Testing process takes about 1-2 hours**

  - Positive blood culture bottle
  - Gram stain
  - Incubation 0h - 12-24h
  - Automated Testing Set-Up 12-24h
  - Automated Organism ID 12-48h
  - Automated Susceptibilities
  - Patient care team sees ID and susceptibility results

Nanosphereus.com: Jan 2015
**Nucleic Acid Amplification (Verigene™)**

- **Advantages**
  - Multiplex technology: organism ID and select resistance genes
  - Can escalate and de-escalate therapy for Staphylococcus

- **Disadvantages**
  - Product is an add-on, and doesn’t replace current technology for organism ID or susceptibility
  - Diminished sensitivity and specificity directly from specimen

---

**MALDI-TOF**

- **Matrix-Assisted Laser Desorption/Ionization-Time Of Flight**
  - Utilizes mass spectrometry
  - Identifies bacteria based on unique protein sequences
  - Process for organism identification takes ~1 hour
  - Widely used in Europe, gaining popularity in the US

---

MALDI-TOF

Isolation of bacterial colony and dilution

Extraction and addition of matrix

Ionization, vaporization and travel up TOF tube

MALDI-TOF

Laser irradiation

Sample currently being tested

Time of flight

Red spectra: sample to be identified

Blue spectra: match from library
MALDI-TOF and Detection of MRSA

- 20 isolate analysis identified unique profile for MRSA vs. MSSA
Timeline for Organism Identification with MALDI-TOF compared with Automated Testing

MALDI-TOF

- **Advantages**
  - Reduced time to organism ID by 24-36 hours
  - Can replace conventional or automated systems for organism identification for most organisms
  - Very low reagent cost

- **Disadvantages**
  - Costly initial investment
  - Currently limited clinical utility in detecting methicillin resistance
PNA-FISH™, Quick-FISH™, Xpress-FISH™
PNA-FISH™, Quick-FISH™, Xpress-FISH™

- **Products:**
  - Staphylococcus (*S. aureus* vs. Coag-neg Staph)
    - *MecA* probe
  - Enterococcus (*E. faecalis* vs. *E. faecium* vs. other Enterococcus)
  - GNR (Pseudomonas, Klebsiella, *E. coli*, vs. other GNR)
  - Candida (*C. albicans*, *C. glabrata* vs. *C. parapsilosis*)

**Timeline for Organism Identification with FISH Technology**

- **Testing process takes 20 min-2 hours**
**PNA-FISH™, Quick-FISH™, Xpress-FISH™**

**Advantages**
- Extremely quick testing process (Quick-FISH™)
- Excellent clinical experience with the product
- Proven clinical benefits

**Disadvantages**
- Current products are limited to three targets
- Limited ability to detect resistance mechanisms
- Moderately complex methodology for micro technicians

---

**Accelerate™**

**Rapid 2-step process for organism ID, and select MIC and sensitivities**
**Accelerate™**

- *S. aureus* antibiotic susceptibility testing and MICs for the following:

<table>
<thead>
<tr>
<th>FDA Approved</th>
<th>Research Use Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline</td>
<td>Trimethoprim/Sulfa</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Doxycyline</td>
</tr>
<tr>
<td>Daptomycin</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td>MRSA (via cefoxitin)</td>
<td></td>
</tr>
</tbody>
</table>

**Accelerate™**

- PNA-FISH™ takes about 20 min
- Accelerate PhenoTest™ takes about 7 hours
Accelerate™

• **Advantages**
  – Only product to offer rapid organism ID, MICs and sensitivities
  – Select sensitivities 1.5-2.5 days sooner

• **Disadvantages**
  – Platform has limited capabilities to handle large number of samples
  – Currently limited number of antibiotics on panel
  – Slower time to methicillin-resistance than other technologies

---

**Summary of Early Organism Identification or Detection of Resistance**

• Technologies can identify organism and/or mecA 1.5-2.5 days quicker than convention methods
  • Mass spectrometry: MALDI-TOF
  • Nucleic acid hybridization: PNA-FISH™
  • Nucleic acid amplification: PCR, Multiplex arrays

• Tests have highest sensitivity/specificity from blood or isolated culture, but can be performed on any specimen
### S. aureus Clinical Outcomes Studies Linked with Rapid Diagnostics

<table>
<thead>
<tr>
<th>Study</th>
<th>RDT/pathogen(s)</th>
<th>Study Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ly, 2008</td>
<td>PNA-FISH S. aureus vs GPCs</td>
<td>RDT and pre/post AST</td>
<td>↓ inappropriate abx use by 2.5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ mortality (17% vs 8%)</td>
</tr>
<tr>
<td>Carver, 2008</td>
<td>RT-PCR meca (MRSA)</td>
<td>meca gene reporting and pre/post AST</td>
<td>↓ time to optimal abx (64.7h vs 39.9h), ↓ duration of bacteremia</td>
</tr>
<tr>
<td>Wong, 2010</td>
<td>rPCR S. aureus</td>
<td>Pre/post intervention: RDT + AST</td>
<td>↓ LOS (21.5d vs 15.3d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Cost by $21,387 per patient</td>
</tr>
<tr>
<td>Box, 2015</td>
<td>Microarray Gram-Positive</td>
<td>Pre/post intervention: RDT + AST</td>
<td>↓ Time to Appropriate Abx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ LOS (9.1 vs. 7.2 days)</td>
</tr>
<tr>
<td>Revolinski, 2015</td>
<td>Microarray Gram-Positive</td>
<td>Pre/post intervention: RDT + AST</td>
<td>↓ Cost ($17,530 vs. $10,290)</td>
</tr>
<tr>
<td>Beal, 2015</td>
<td>Microarray Gram-Positive</td>
<td>Pre/post intervention: Nursing driven algorithm</td>
<td>↓ Time to Appropriate Abx</td>
</tr>
</tbody>
</table>

### Incorporating Rapid Diagnostics into a Comprehensive Disease Management Approach

- **Despite early targeted therapy, morbidity and mortality remains significant**
- **Potential improvements in the areas of:**
  - Identification of complicated bacteremia
  - Surgical management
  - Antibiotic regimen(s)
  - Medical management
  - Process improvements
  - Basic knowledge
## Compliance with Performance Measures for S. aureus bacteremia

<table>
<thead>
<tr>
<th>Performance Measure</th>
<th>Compliance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up blood cultures to document clearance</td>
<td>61.2</td>
</tr>
<tr>
<td>Source control</td>
<td>70.2</td>
</tr>
<tr>
<td>Echocardiogram for high risk patients</td>
<td>52.8</td>
</tr>
<tr>
<td>Early beta-lactam therapy for MSSA</td>
<td>56.9</td>
</tr>
<tr>
<td>Appropriate vancomycin serum concentration</td>
<td>46.9</td>
</tr>
<tr>
<td>Appropriate treatment duration</td>
<td>72.9</td>
</tr>
</tbody>
</table>


## Comprehensive Collaborative Approach to Improving Outcomes with S. aureus Bacteremia

- **Initiate empiric antibiotics**
- **Recommend obtaining cultures until clearance**
- **If MSSA, recommend β-lactam therapy**
- **Make antibiotic adjustments, if necessary**

**Pharmacy** receives real-time alerts for positive blood cultures, speciation, and susceptibilities from **Microbiology**

- **Optimize vancomycin dosing & levels**
- **Reassess therapy at 72 hours and 5 days**

**GPC in clusters**

- **S. aureus identification via MALDI-TOF**
- **Susceptibilities**

- **Recommend ID Consultation**
- **Eliminate foci of infection, obtain echo if complicated bacteremia, prescribe appropriate duration of therapy**
Collaborative Approach to Improving Outcomes

Management of *Staphylococcus aureus* Bacteremia: A Guide for the ID Consult Service

1. Timely initiation of effective antibiotics following gram stain with GPCs in clusters
2. Timely change to β-lactam therapy if MSSA
   - Nafcillin for endocarditis or meningitis
   - Cefazolin for patient without endocarditis or meningitis
3. Therapeutic vancomycin level
   - 15-20 mg/L for endocarditis, meningitis or vertebral osteomyelitis
   - 10-15 mg/L for uncomplicated bacteremia
4. Obtain repeat blood cultures every 24-48 hours until documented clearance of bacteremia
5. Identify and control source of bacteremia
6. Echocardiography
7. Assess for potential treatment failure and adjust antibiotics
   - See reverse for recommended antibiotic adjustments
8. Treatment duration
   - Uncomplicated bacteremia: 2 weeks
   - Complicated bacteremia without endocarditis or osteomyelitis: at least 4 weeks
   - Complicated bacteremia with endocarditis: at least 6 weeks
   - Complicated bacteremia with osteomyelitis: at least 8 weeks

Uncomplicated bacteremia definition: no endocarditis, no implanted prostheses, no evidence of metastatic sites of infection, repeat blood cultures 2-4 days are negative, AND defervescence within 72 hours of therapy

Overall Bundle Compliance to Quality Performance Measures for *S. aureus* Bacteremia

<table>
<thead>
<tr>
<th>Intervention Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>84.1</td>
<td>56.1</td>
</tr>
</tbody>
</table>

*P* < 0.001

### Compliance with Individual Performance Measures for *S. aureus* Bacteremia

<table>
<thead>
<tr>
<th>Performance measure</th>
<th>Historic Group</th>
<th>Intervention Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic initiation within 24 hrs</td>
<td>97.5%</td>
<td>98.9%</td>
<td>0.612</td>
</tr>
<tr>
<td>Document clearance of cultures</td>
<td>85.0%</td>
<td>96.5%</td>
<td>0.013</td>
</tr>
<tr>
<td>Appropriate duration of therapy</td>
<td>86.4%</td>
<td>94.9%</td>
<td>0.088</td>
</tr>
<tr>
<td>IV Beta-lactam therapy for MSSA</td>
<td>86.8%</td>
<td>94.0%</td>
<td>0.321</td>
</tr>
<tr>
<td>Appropriate vancomycin trough</td>
<td>93%</td>
<td>97.6%</td>
<td>0.616</td>
</tr>
<tr>
<td>Echo for complicated bacteremia</td>
<td>96.2%</td>
<td>96.7%</td>
<td>0.999</td>
</tr>
<tr>
<td>Source control</td>
<td>78.6%</td>
<td>97.2%</td>
<td>0.037</td>
</tr>
</tbody>
</table>


### Outcomes for *S. aureus* Bacteremia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Historic Group</th>
<th>Intervention Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>19.5%</td>
<td>11.4%</td>
<td>0.200</td>
</tr>
<tr>
<td>Length of stay, from bacteremia (IQR)</td>
<td>9 (5-17)</td>
<td>9 (5-20)</td>
<td>0.474</td>
</tr>
<tr>
<td>30-Day readmission with <em>S. aureus</em> bacteremia</td>
<td>11.0%</td>
<td>1.1%</td>
<td>0.008</td>
</tr>
<tr>
<td>Persistent Bacteremia</td>
<td>13.4%</td>
<td>9.1%</td>
<td>0.467</td>
</tr>
</tbody>
</table>

### Comprehensive Management of *S. aureus* Bacteremia

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lopez-Cortes, 2013</strong>&lt;br&gt;(n=508)</td>
<td>Multicenter pre-post study: Develop guideline: ID consult and Compliance with 6 bundle process measures</td>
<td>14-day mortality: 17.8% vs 11.3%, Adjusted 14-day mortality: OR 0.49 (0.28-0.87), p=0.016</td>
</tr>
<tr>
<td><strong>Saunderson, 2014</strong>&lt;br&gt;(n=66)</td>
<td>Pediatric guideline, and intervention to promote compliance with 4 process measures</td>
<td>Length of stay: 14 days vs 16.5 days, Ns 30-day mortality: 0% vs 8.6%, Ns</td>
</tr>
<tr>
<td><strong>Borde, 2014</strong>&lt;br&gt;(n=59)</td>
<td>Develop guideline and promote compliance with bundle process measures</td>
<td>In-hospital mortality: 43.6% vs 10.0%, p=0.009</td>
</tr>
<tr>
<td><strong>Nagao, 2017</strong>&lt;br&gt;(n=477)</td>
<td>Single center retrospective analysis of compliance with 5 bundle endpoints</td>
<td>Adherence to ≥ four measures: increased from 47.5 % in 2006 to 79.3 % in 2014 (P = 0.001); the 30-day mortality decreased from 10.0 to 3.4%</td>
</tr>
<tr>
<td><strong>Wenzler, 2017</strong>&lt;br&gt;(n=89)</td>
<td>Automated pharmacist driven intervention to improve compliance with performance measures</td>
<td>All cause mortality: (15.6% vs. 2.6%, P=0.063)</td>
</tr>
</tbody>
</table>

### Conclusion

- Rapid diagnostics can dramatically improve time to organism identification and detection of some resistance genes
- Developing a process to facilitate timely antibiotic changes following rapid diagnostics is essential
- Developing a comprehensive approach can optimize outcome
Utility of Rapid Diagnostics in 
*S. aureus* Bacteremia in 
Antimicrobial Stewardship Programs

Jerod Nagel, PharmD, BCPS (AQID)  
Pharmacy Team Lead, Infectious Diseases  
Director Infectious Disease Residency  
Clinical Assistant Instructor  
Michigan Medicine  
University of Michigan, College of Pharmacy